Similarities between Tropical Spastic Paraparesis (TSP) and neurolathyrism

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Tropical Spastic Paraparesis
Tropical Spastic Paraparesis (TSP) is a slowly progressive spastic paraparesis with an insidious onset in adulthood. It has been found all around the world (except in the poles), mainly in tropical and subtropical regions. It affects more women than men (almost 2:1) of low socioeconomic classes.

In 1985 French investigators discovered the association of TSP with HTLV-I, a retrovirus discovered in USA in 1980. A few months after the French publication in 1985 TSP was also associated with HTLV-I in Colombia and Jamaica. In 1986 Japanese researchers published the association of HTLV-I with a similar syndrome and named the disease as HAM (HTLV-I Associated Myelopathy). Since 1988 the World Health Organization (WHO) recommended the conciliatory name TSP/HAM to both syndromes. Until the end of 1996 only 45% (1,261 of 2,811 cases) of TSPs were associated to HTLV-I. That means that more (55%) of TSPs remained idiopathic or at least HTLV-I seronegative.

Neurolathyrism
Neurolathyrism is a neurologic disorder caused by excessive ingestion of Lathyrus species. Lathyrism has been known since ancient times; epidemics have occurred in some regions, including Russia, southern Europe, the Middle East and India, particularly during times of famine. At these times increased consumption of Lathyrus sativus, L. cicera and Vicia sativa has been implicated. Horses, cattle, swine and birds have been affected.

Clinically, lathyrism often presents relatively rapidly after a prolonged period (months) of ingesting large amounts of the grain, often in the context of general malnutrition. Disease often commences with complaints of pain or cramps in the legs or in the region of the lumbar spine. Lower extremity weakness and sphincter dysfunction then develop, soon evolving into permanent spastic paraparesis. The cramping pains and the sphincter dysfunction usually subside when the intoxication ceases and spasticity develops.

There are a few pathologic studies of lathyrism, but a report by Hirano et al. confirms earlier descriptions of bilateral atrophy in the distal pyramidal tract in the lumbar cord. Additionally, there have been morphologic descriptions of degenerative changes in the spinocerebellar tracts and dorsal columns. In concert, these data suggest a central nervous system (CNS) disease expressed most pronouncedly in the distribution of the longest CNS fibres.

Konzo or Buka-Buka is an acute or chronic form of spastic paraparesis more common in tropical countries than in temperate climates. Deficiencies or toxicities due to primitive diets as well as infectious agents have been implicated. Konzo is similar to lathyrism but differs from TSP/HAM and from lathyrism in its abrupt onset, nonprogressive course. Normal magnetic resonance imaging scans of brain and spinal cord in severely affected patients provide evidence of selective damage of the upper motor neurons. All Konzo patients were seronegative to retroviruses.

Neurolathyrism affects more men and is usually epidemic whilst TSP/HAM affects more women and it is usually endemic. These are the some of the most important differences between two similar clinical and neuropathological syndromes.

From the clinical point of view both TSP/HAM and neurolathyrism depict a pyramidal syndrome affecting
mainly the corticospinal pathways and in a lesser grade the sensory and spinocerebellar pathways of the spinal cord.

Neuropathology of TSP/HAM
The clinicopathological studies\textsuperscript{10} show that TSP/HAM has a clearly defined pathological pattern. The clinical differences in TSP/HAM patients are related to the extension and severity of this pattern. The cases showed a close clinicopathological correlation. All of them had lesions in the axons and myelin of the pyramidal tract of the spinal cord. This followed an ascendant pattern similar to some degenerative diseases, as in familiar spastic paraparesis, with marked abnormalities in the lumbar and thoracic segments of the spinal cord that became less severe as the tract reached the cervical segments. Most cases had lesions in the Goll’s tract distributed in a descendant pattern, with maximal involvement in the cervical region and becoming negligible towards the caudal regions.

The spinal cord lesions of patients with TSP/HAM, ascendant in the pyramidal tract and descendant in the posterior columns, have been interpreted as demyelinating, either as a primary cytotoxic disorder or secondary to inflammatory or immunological disorders. However, primary demyelinating diseases, either viral or inflammatory in origin, damage myelin in several areas, usually confluently and in a transverse fashion. Disorders that damage the myelin affect different systems simultaneously, such as multiple sclerosis or multifocal leukoencephalopathy. Central nervous system demyelinating diseases involve groups of oligodendrocytes, and each oligodendrocyte myelinates several axons independent of their functions. However, in TSP/HAM lesions, the myelin follows the axons in a dying-back fashion (axial) that especially affects the longest axons. The lesions in the posterior columns also support the idea of an axomyelinic degeneration. The lesions of Goll’s tract in the cervical spinal cord are selective, affecting the longest axons from the legs.

It seems unlikely that these parenchymal changes are secondary to vascular changes. Abnormal vessels with gross thickening of the adventitia were seen in all patients, many of them with lymphocytic cuffs, especially in the spinal cord, brain stem, midbrain, thalamus, and meninges, but were unrelated to the location or severity of the parenchymal damage. Furthermore, vascular changes are restricted to a proliferation on the adventitia and no vasculitic changes such as necrosis of the vascular wall, endothelial proliferation, or ischemic lesions in the surrounding tissue were found\textsuperscript{10}.

Neuropathology of neurolathyrism
“Comprehension of lathyrism has been made more difficult by the absence of a complete neuropathological study using contemporary histopathological techniques. Studies of the brain are lacking, save for one case of a subject who developed the disorder 31 years prior to death in whom loss and shrinkage of pyramidal neurons in the upper part of the precentral gyrus was noted. The balance of neuropathological studies has focused on the spinal cord, which shows predominantly distal symmetrical degeneration of lateral and ventral corticospinal tracts, sometimes with distal degeneration of spinocerebellar and gracile tracts. One Rumanian subject, who died with mildly atrophic leg muscles 32 years after the development of moderately severe lathyrism, showed distal axonal degeneration of the fasciculus gracilis and spinocerebellar pathways and changes in (but not loss of) lumbar anterior horn cells, including swelling, diminished Nissl substance, and Hirano bodies.

There are at least two interpretations of these changes. One possibility is that lathyrism is a central distal axonopathy dominated by degeneration of the longest corticospinal tracts, with lesser involvement of shorter pyramidal pathways serving the upper extremities of the most severely compromised individuals. This interpretation is consistent with the neurophysiological and neuropathological findings, except perhaps the loss of upper motor neurons\textsuperscript{11}.

Conclusions
TSP/HAM and neurolathyrism have clinical and neuropathological similarities which suggest a common or similar cause, possible of toxometabolic origin. Cassava (manioc, mandioca) consumption, the etiological trigger of Konzo in the setting of minimal nutrition (sulphur deficiency) is rapidly expanding in the tropics and subtropics and appears to be a strong candidate for some TSPs in HTLV-I seronegative populations. There is a possible relation of atypical
parkinsonism in the French West Indies with consumption of tropical plants like herbal tea and fruits from the Annonaceae family (*Annona muricata* and *A. squamosa*) containing alkaloids that have insecticidal activity. This enhances the idea of chronic neurotoxicity in some degenerative diseases of the central nervous system.

References

Professor Zaninovic highlights similarities between the clinical and neuropathological features of lathyrism and HTLV-1-associated TSP/HAM and, on this basis, suggests a common or similar cause, possibly of toxometabolic origin. This hypothesis is advanced to account for the fact that 55% of TSP/HAM cases are reportedly HTLV-1 seronegative. He further suggests that cassava dependency may be responsible for some cases of spastic paraparesis (Konzo) in HTLV-1 seronegative populations.

The hypothesis stands on a rocky foundation because of the differences between TSP/HAM and the two toxic-nutritional disorders. Whereas Konzo and lathyrism may begin abruptly, improve and then stabilize, TSP/HAM has an insidious onset and is slowly progressive. It is true that Konzo and lathyrism may progress with continued consumption of cassava and grass pea, respectively, but in their absence the diseases are stable for decades. By contrast, clinical advancement is the norm for TSP/HAM, and the neurological picture may include features (sensory, lower motor neuron and cognitive deficits) that are absent in Konzo and lathyrism.

While these facts are solid, there are significant uncertainties in regard to the clinical disorder associated with cassava dependency. Whereas spastic paraparesis (Konzo) in children and women of child-bearing age has been reported in central and southern Africa, cassava-dependent populations in west Africa are more prone to an ataxic myeloneuropathy in middle age. Some of these latter cases may have been counted as TSP/HAM. Whether the differences in age of onset and neurological picture arise from differences in neurotoxin content of cassava-based food is a question that merits prompt investigation. Further, Zaninovic’s proposal correctly implies that viral and non-viral environmental factors may combine to cause the expression of human disease.